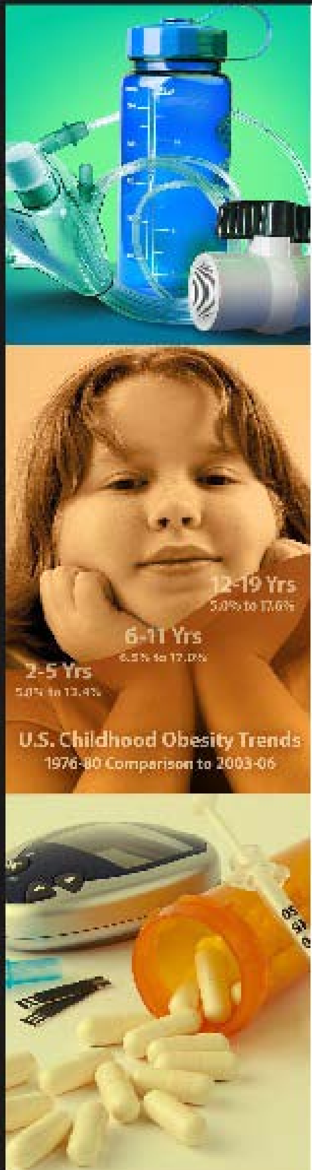
NTP
National Toxicology Program



NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

Research Strategies and Key Data Needs (Group D)

James Kaput (chair)
Kembra Howdeshell (rapporteur)

Crabtree Marriott Hotel
January 11-13, 20111

Research Strategy/Data Needs (Group D) Members

Henry Anderson, Wisconsin Dept. Health & Family Services	Monica Lind, Uppsala U
Bruce Blumberg, UC-Irvine	Jingbo Pi, Hamner Institutes for Health
Chad Blystone, NIH/NIEHS/NTP	Karen Ryan, U Cincinnati
Deborah Clegg, U Texas Southwestern	Ted Schettler, Science & Environment Health Network
Kembra Howdeshell, NIH/NIEHS/NTP (rapporteur)	Evan Simpson, Prince Henry's Institute of Medical Research
Richard Judson, US EPA	Theodore Slotkin, Duke
James Kaput, FDA/NCTR (chair)	Rogelio Tornero-Velez , US EPA

Propose a research strategy to explore the significance of exposures to environmental chemicals in the rising rates of obesity and diabetes, including human, animal and mechanistic studies

- Deep phenotyping
  - Dlassification/subclasses/taxonomy in humans
  - Imaging, fat depot analysis in animals
- Human ecosystems mapping
- Genotyping or inbred – comparative genomics (controversial)
- Sentinel studies of animals in nature

Are there immediate data gaps that if filled would provide significant direction to longer term research programs?

- Discovery science approaches – undirected

Are there new research tools that need to be developed?

- Technologies
  - Data discovery (undirected mass spec metabolites/proteins) MRI for imaging, mass spec, etc.
- Software
  - Measuring exposures
  - Diet
- Databases
  - Nutritional Phenotype db
  - Metadata for studies
- Analytical methods
  - Nonlinear methodologies
  - Creation of models: protein – protein, pathways, networks, cell phenotypes, cell-cell

Bioinformatics

The Journal of Nutrition **140**, 2104 – 2115 (2010)
Commentary

Web-Enabled and Improved Software Tools and Data Are Needed to Measure Nutrient Intakes and Physical Activity for Personalized Health Research[1–3]

Phyllis J. Stumbo,[4*] Rick Weiss,[5] John W. Newman,[6] Jean A. Pennington,[7] Katherine L. Tucker,[8] Paddy L. Wiesenfeld,[9] Anne-Kathrin Illner,[10] David M. Klurfeld,[11] and Jim Kaput[12]

[4]Institute for Clinical and Translational Science, University of Iowa, Iowa City, IA 52242; [5]Viocare, Inc., Princeton, NJ 08542; [6]USDA, Agricultural Research Service, Western Human Nutrition Research Center, Davis, CA 95616; [7]Division of Nutrition Research Coordination, National Institutes of Health, Bethesda, MD 20892 (retired); [8]Department of Health Sciences, Northeastern University, Boston, MA 02115; [9]Division of Toxicology, Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, FDA, Laurel, MD 20708; [10]Department of Epidemiology, German Institute of Human Nutrition, Potsdam-Rehbrücke, 14558 Nuthetal, Germany; [11]USDA Agricultural Research Service, Beltsville, MD 20705; and [12]Division of Personalized Nutrition and Medicine, National Center for Toxicological Research, FDA, Jefferson, AR 72079

Academia | Industry | USDA | NIH | CFSAN | EU | NCTR

Workshop @ USDA Spring ’09 — Organized by NCTR & USDA

Genes Nutr (2010) 5:285–296
DOI 10.1007/s12263-010-0192-8

REVIEW

The Micronutrient Genomics Project: a community-driven knowledge base for micronutrient research

Ben van Ommen · Ahmed El-Sohemy · John Hesketh · Jim Kaput · Michael Fenech · Chris T. Evelo · Harry J. McArdle · Jildau Bouwman · Georg Lietz · John C. Mathers · Sue Fairweather-Tait · Henk van Kranen · Ruan Elliott · Suzan Wopereis · Lynnette R. Ferguson · Catherine Méplan · Giuditta Perozzi · Lindsay Allen · Damariz Rivero · The Micronutrient Genomics Project Working Group

Genes Nutr (2010) 5:189–203
DOI 10.1007/s12263-010-0167-9

REVIEW

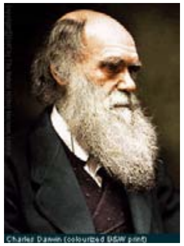
Challenges of molecular nutrition research 6: the nutritional phenotype database to store, share and evaluate nutritional systems biology studies

Ben van Ommen · Jildau Bouwman · Lars O. Dragsted · Christian A. Drevon · Ruan Elliott · Philip de Groot · Jim Kaput · John C. Mathers · Michael Müller · Fre Pepping · Jahn Saito · Augustin Scalbert · Marijana Radonjic · Philippe Rocca-Serra · Anthony Travis · Suzan Wopereis · Chris T. Evelo

Basis of Nutrigenomics

A different effect of a *genotype* on disease in persons with different *environmental* exposures

Genotype X Environment Interactions



A different effect of an *environmental* exposure on disease risk in persons with different *genotypes*

Ottman, *Prev. Med* 25, 764 (1996)

Statistical Parlance	**The *main effect(s)* may be *genotype x environment interaction(s)* for chronic diseases and modifying effects**

Hypolactasia

N. European
Indian children
Afr American children
Indian adults
Mex American - adult
Cretans
Cypriots
N. American Jews
Mexicans - rural
Afr American - adult
Eskimo
Asian Americans
SE Asians

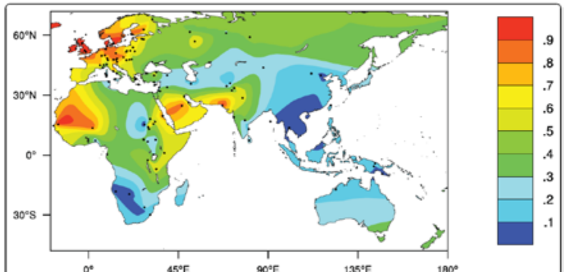
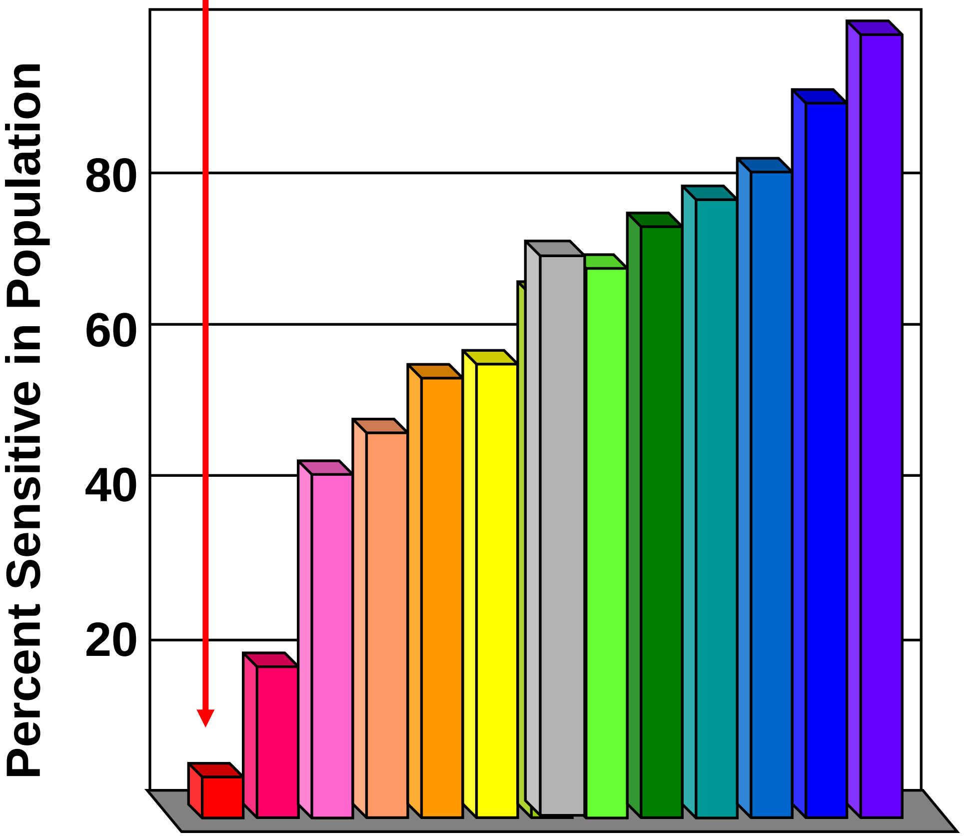


Figure 1 Interpolated map of Old World LP phenotype frequencies. Dots represent collection locations. Colours and colour key show the frequencies of the LP phenotype estimated by surface interpolation.

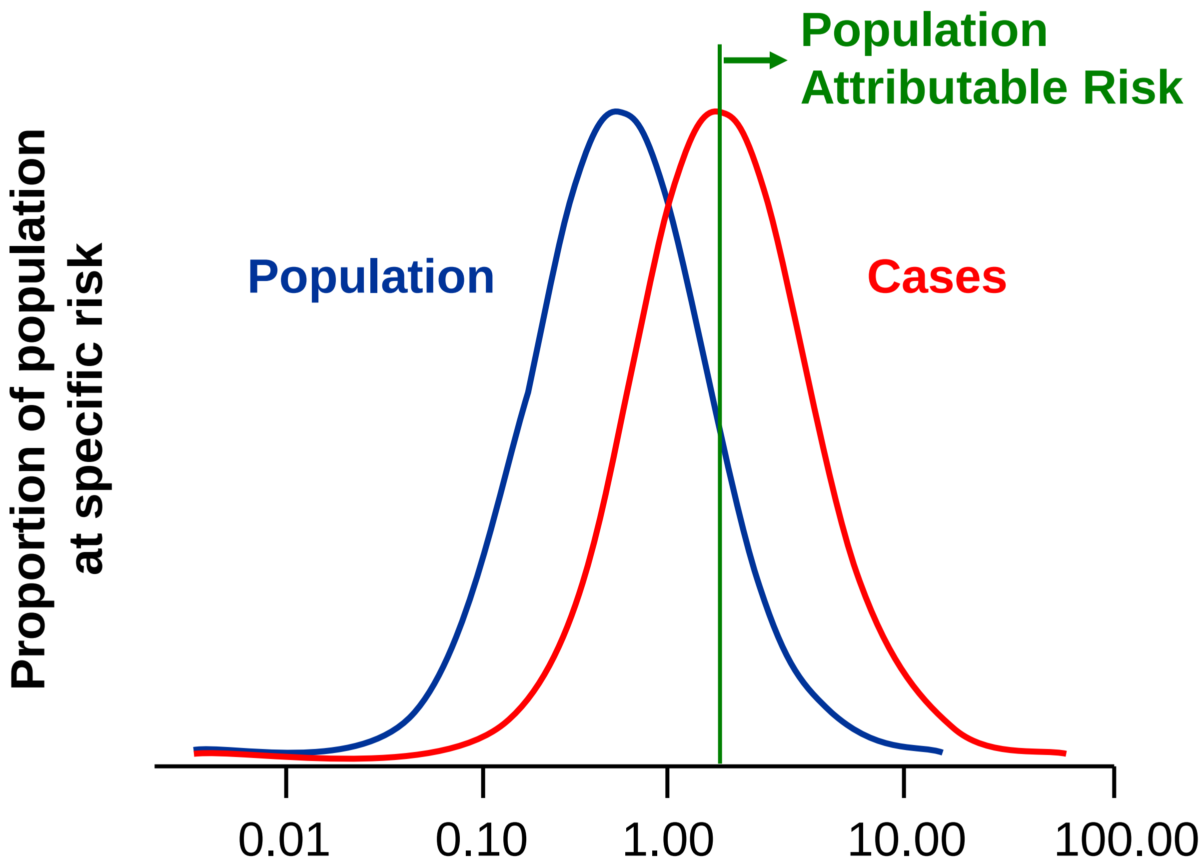
Itan *et al. BMC Evolutionary Biology* 2010, **10**:36
http://www.biomedcentral.com/1471-2148/10/36

C-13910T In Africa: G-14010C



Kaput and Rodriguez, *Physiological Genomics* 16, 166 (2004)

The Questions for Personalizing Healthcare



Why is there a distribution of health within a population ?

Why is there a distribution within cases (disease)?

Is risk as calculated for population useful for the individual??

What path to knowledge??

http://science.cancerresearchuk.org/cri/research/population_studies/?version=2

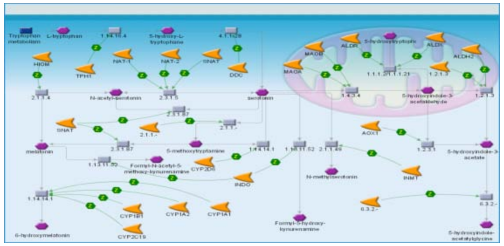
The Diversity Challenges

Nutritional

Composition of agri-foods varies

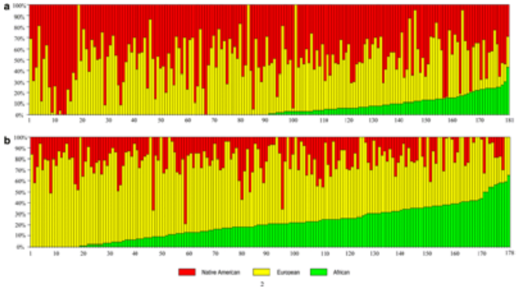
Culture & food preparation

Food processing



Health & Disease

Variable pathways to each



Genetic

Humans are the same but different

History & culture alter populations

Kaput et al, *NMCVD* 17, 89 (2007)

T2DM Treatment Strategies

Pharmacologic intervention required if glycemic control not achieved with diet and exercise within 3 months

~85% require interventions

Pancreas
Liver
Intestine
Adipose

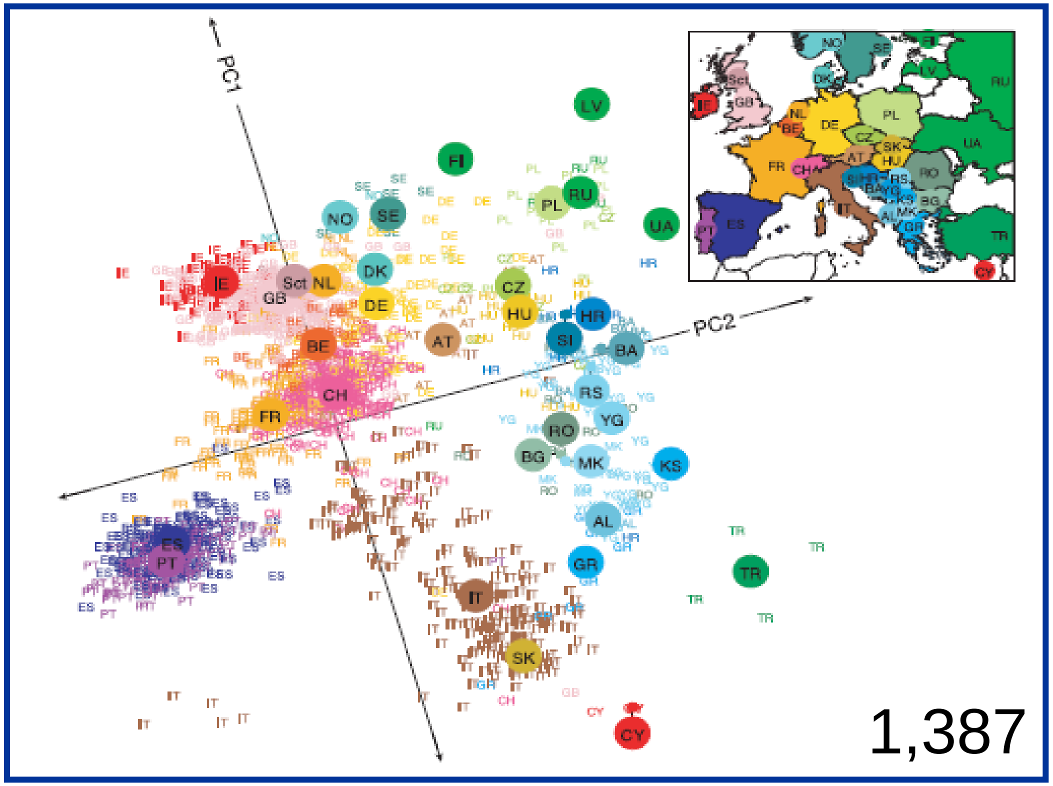
[1] http://www.aafp.org/PreBuilt/monograph_diabetestreatment.pdf

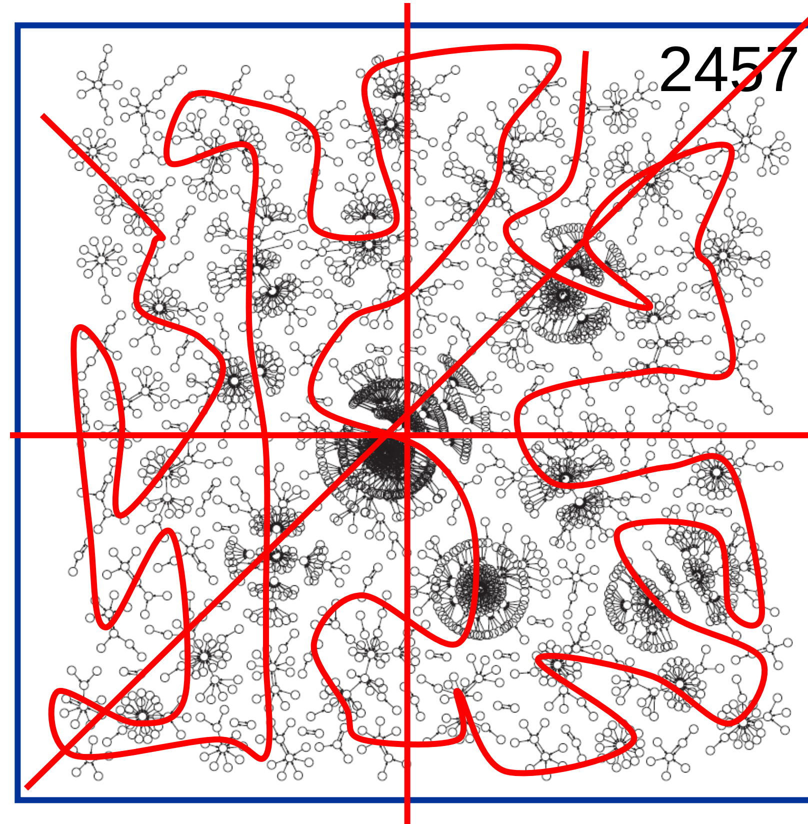
[2] ~10% failure/yr

Drug	Target	Effective [1]
Sulfonylurea	T2DM < 5yr	~50% [2]
Meglitinides	T2DM < 5yr & Elevated PPG	?
Biguanide	Obese insulin resistant	~75%
α-Glucosidase inhibitor	Elevated postprandial glucose (PPG)	2nd line
Thiazolidinediones	Obese insulin resistant	2nd line

Kaput et al, *Pharmacogenomics* 8, 369 (2007)

Can Cases Be Matched to Controls?





Novembre et al *Nature* 456, 98 (2008)

Lu et al *EJHG* 17, 967 (2009)

1000 Genomes: 300 – 400 variants affecting 250 – 300 genes resulting in loss of function (LOF) per person

Global Initiatives

DPNM Roles

Connect genomics to nutrigenomics

Connect lifestyle to genomics

Genes Nutr (2010) 5:275–283
DOI 10.1007/s12263-010-0186-6

COMMENTARY

Connecting the Human Variome Project to nutrigenomics

Jim Kaput · Chris T. Evelo · Giuditta Perozzi ·
Ben van Ommen · Richard Cotton

SPECIAL ARTICLE

Human Mutation

OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY
www.hgvs.org

Human Mutation **30,** 496 – 510 (2009)

Planning the Human Variome Project: The Spain Report*

Jim Kaput,[1†‡] Richard G.H. Cotton,[2,3†] Lauren Hardman,[2†] Michael Watson,[4†] Aida I. Al Aqeel,[5]
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Inge T. Bernstein,[12] Jong Bhak,[13] Stacey L. Bleoo,[14] Helmut Blöcker,[15] Steven E. Brenner,[16] John Burn,[17]
Mariona Bustamante,[18] Rita Calzone,[19] Anne Cambon-Thomsen,[20] Michele Cargill,[21] Paola Carrera,[22] Lawrence Cavedon,[23]
Yoon Shin Cho,[24] Yeun-Jun Chung,[25] Mireille Claustres,[26] Garry Cutting,[27] Raymond Dalgleish,[28] Johan T. den Dunnen,[29]
Carlos Díaz,[30] Steven Dobrowolski,[31] M. Rosário N. dos Santos,[32] Rosemary Ekong,[33] Simon B. Flanagan,[34] Paul Flicek,[35]
Yoichi Furukawa,[36] Maurizio Genuardi,[37] Ho Ghang,[13] Maria V. Golubenko,[38] Marc S. Greenblatt,[39] Ada Hamosh,[40]
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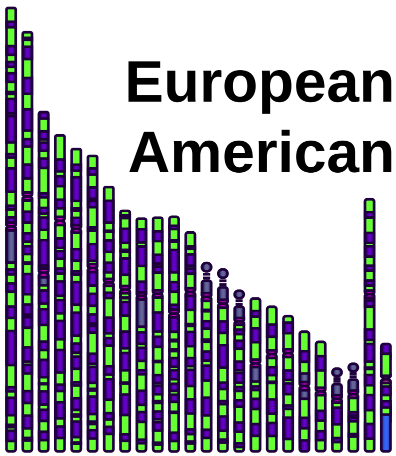
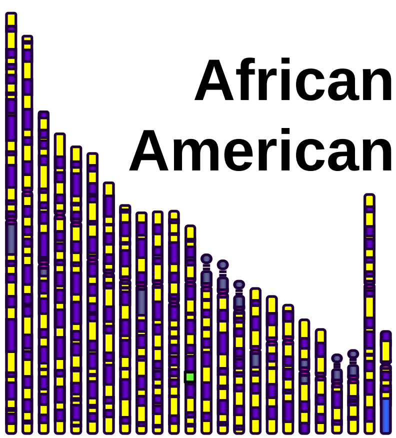
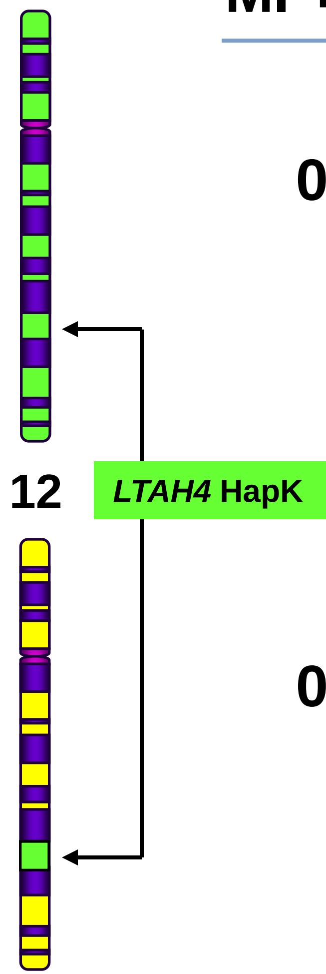
Jong-Young Lee,[24] Vera L. Gil-da-Silva-Lopes,[50] Finlay A. Macrae,[51] Donna Maglott,[52] Makia J. Marafie,[53]
Steven G.E. Marsh,[54] Yoichi Matsubara,[55] Ludwine M. Messiaen,[56] Gabriela Möslein,[57] Mihai G. Netea,[58]
Melissa L. Norton,[59] Peter J. Oefner,[60] William S. Oetting,[61] James C. O'Leary,[62] Ana Maria Oller de Ramirez,[63]
Mark H. Paalman,[64] Jillian Parboosingh,[65] George P. Patrinos,[66] Giuditta Perozzi,[67] Ian R. Phillips,[68] Sue Povey,[34]
Suyash Prasad,[69] Ming Qi,[70] David J. Quin,[71] Rajkumar S. Ramesar,[72] C. Sue Richards,[73] Judith Savige,[74]
Dagmar G. Scheible,[75] Rodney J. Scott,[76] Daniela Seminara,[77] Elizabeth A. Shephard,[78] Rolf H. Sijmons,[79] Timothy D. Smith,[2]
María-Jesús Sobrido,[80] Toshihiro Tanaka,[81] Sean V. Tavtigian,[82] Graham R. Taylor,[83] Jon Teague,[84] Thoralf Töpel,[85]
Mollie Ullman-Cullere,[86] Joji Utsunomiya,[47] Henk J. van Kranen,[87] Mauno Vihinen,[88] Elizabeth Webb,[2] Thomas K. Weber,[89]
Meredith Yeager,[90] Young I. Yeom,[91] Seon-Hee Yim,[92] and Hyang-Sook Yoo,[93] on behalf of contributors to the Human
Variome Project Planning Meeting

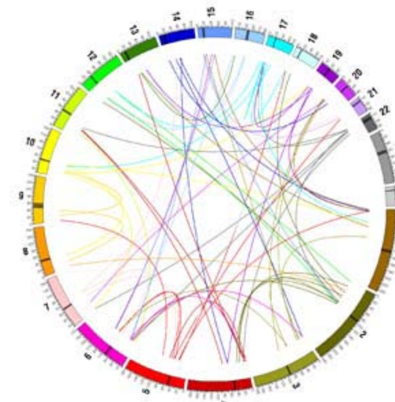
LTH4A HapK and Myocardial Infarction & CVD

Ancestral Group	Frequency of HapK: MI + CVD	Frequency of HapK: Control	Rel Risk	PAR
European American	0.19	0.15	1.35	0.09
African American	0.18	0.04	4.94	0.22



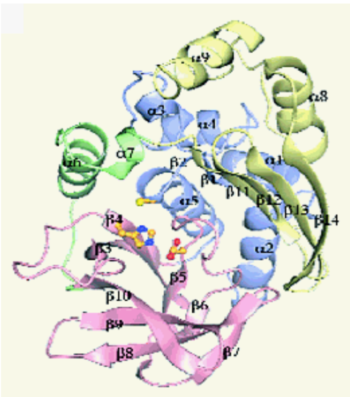






Helgadottir et al *Nature Genetics* 38, 68 2006

The Biochemical Analogy



Units of enzyme activity

To compare preparations, need reference units

Units of anzyme activity / mg protein

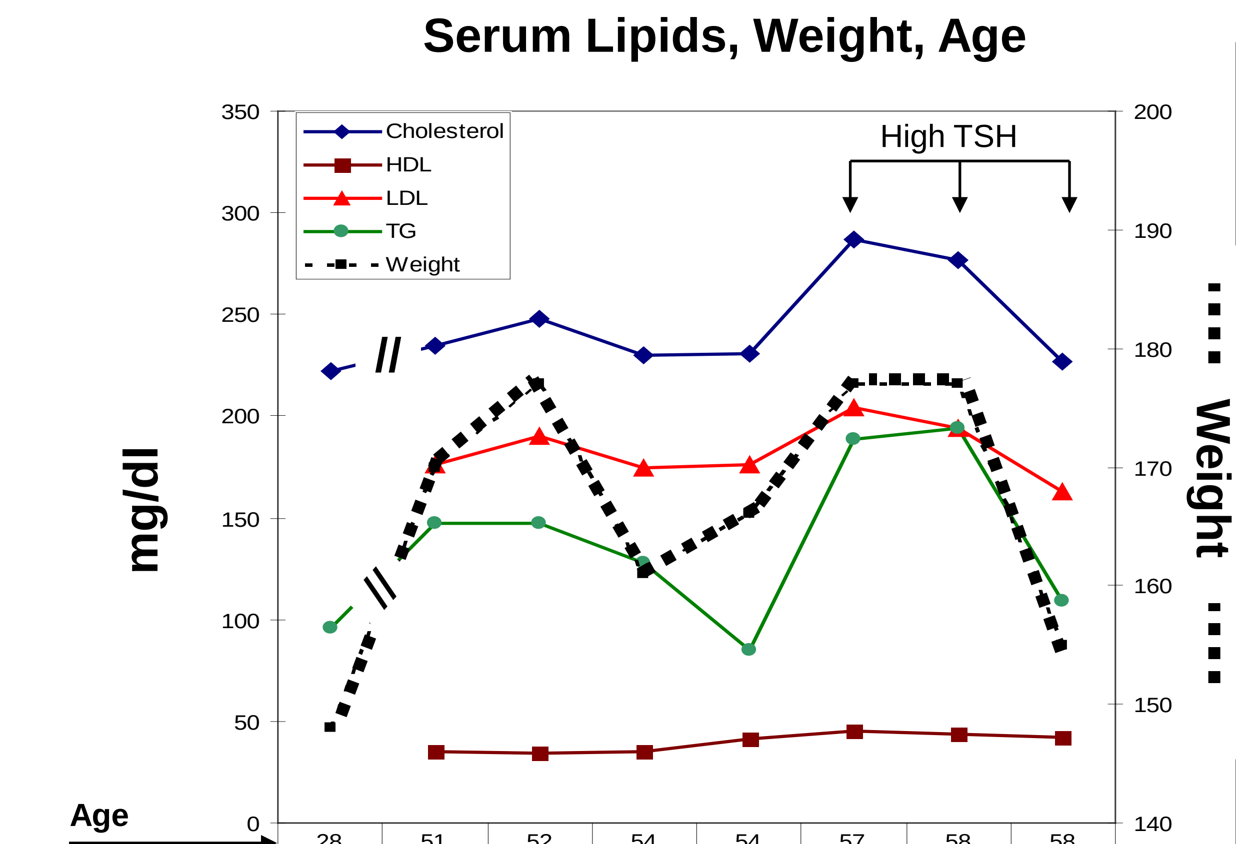
Allele 1	Allele 2
C-G	C-G
A-T	A-T
A-T	A-T
T-A	T-A
G-C	G-C
G-C	A-T
T-A	T-A
T-A	T-A
G-C	G-C
C-G	C-G

Geneticists (and others) use

SNP as absolute indicator/predictor

SNP / Genomic makeup

(Same for metabolites, e.g., HDL)



Age	28	51	52	54	54	57	58	58
Cholesterol	222	235	248	230	231	287	277	227
HDL		35	34	35	41	45	44	42
LDL		176	190	175	176	204	194	163
TG	96	147	147	128	85	189	194	109
Weight	148	170	177	161	166	177	177	155

Age

Which values define health?

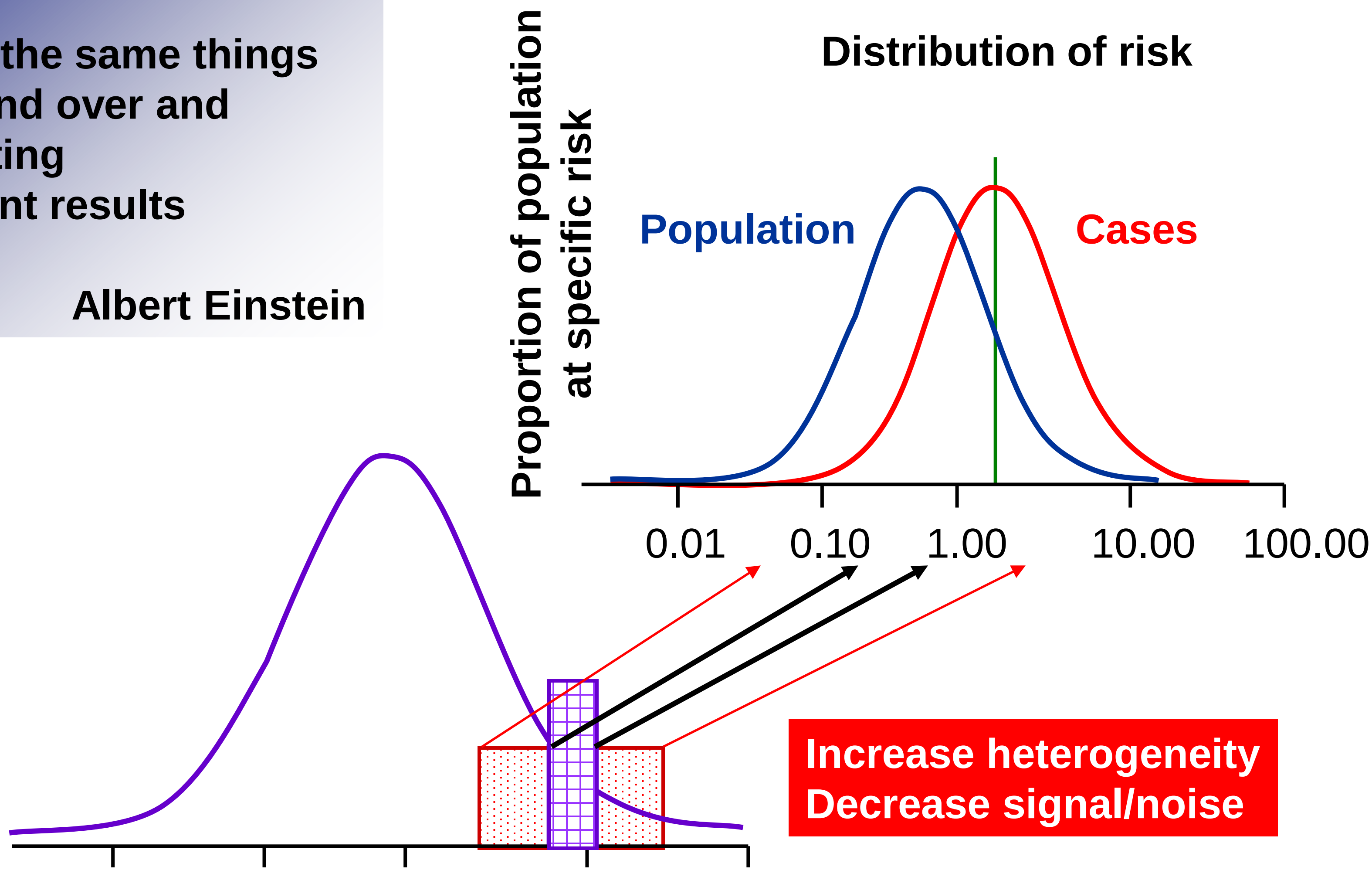
The need for analyses over time

The Logic

Insanity

Doing the same things over and over and expecting different results

Albert Einstein



Human genetic, nutritional, physiological variations

Directed acyclic graph

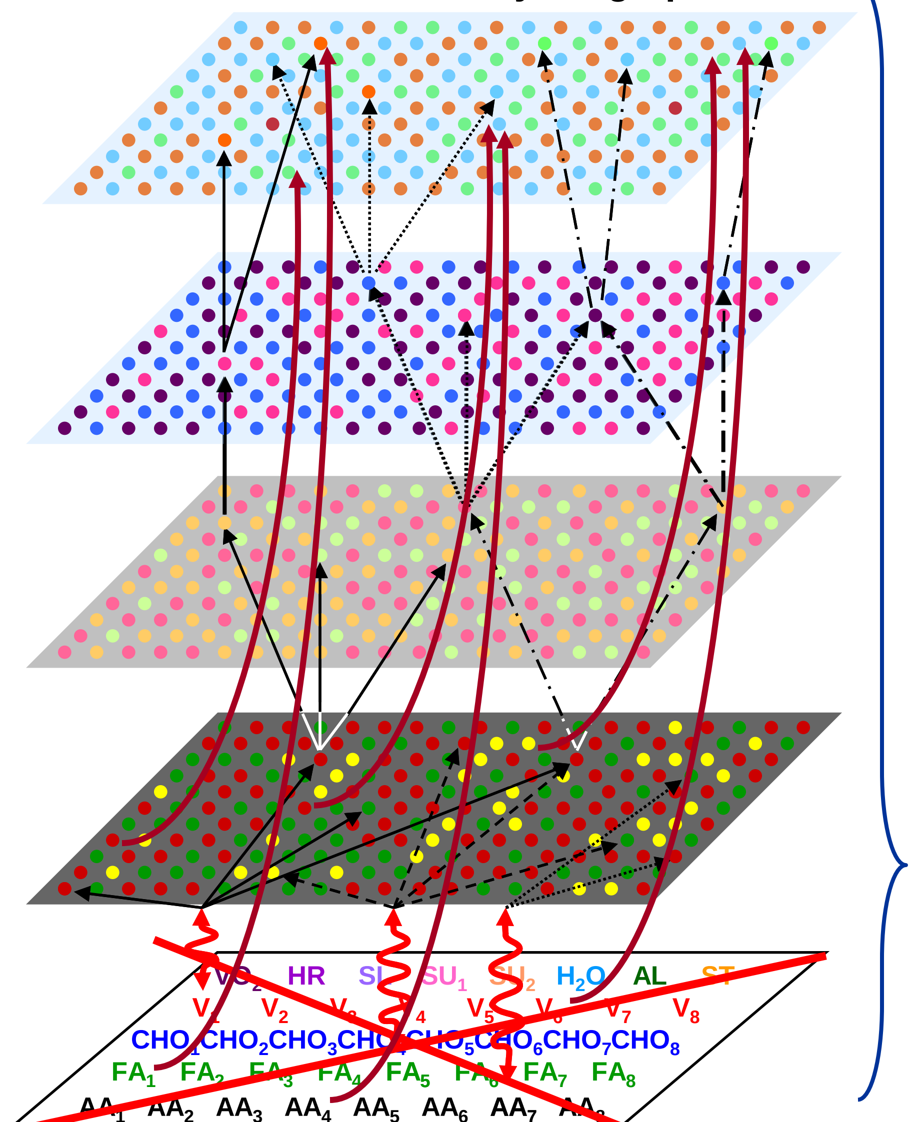
Clinical & Metabolomics

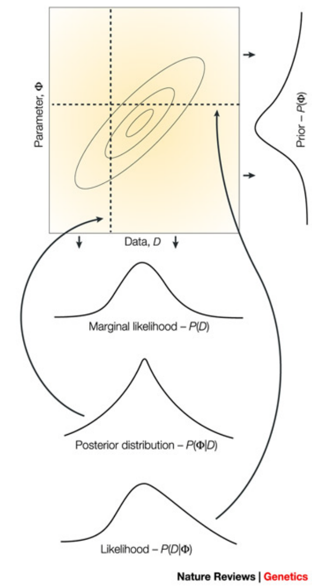
Proteomics

Transcriptomics

Genomics & Epigenomics

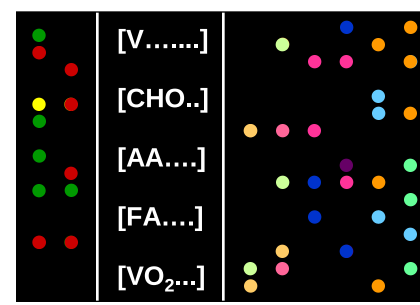
Diet & Lifestyle





NRG 5:251 (2004)

$\int \sum (G \times E)$ | Group



Discovery Science

Dimensionality reduction + classification algorithms

New: A1, B1, B2, C1, C2 = Genotype X Environment Interactions

Old: A, B, C = single genes or GWA, no environment (1,2)

Summary of Experimental Strategy

Deep phenotyping of *response* to intervention or acute challenge

Sequence (candidate) genes with epigenetic analyses in many populations (eventually exome)

Whole genome scans for epistasis and epigenetics

Quantify before data reduction and classification

Propose: Strategy for National and International Projects

Summary: The Process

Local

International

Recruit collaborators - populations

Harmonize protocol

Secure regional funding: distributive science

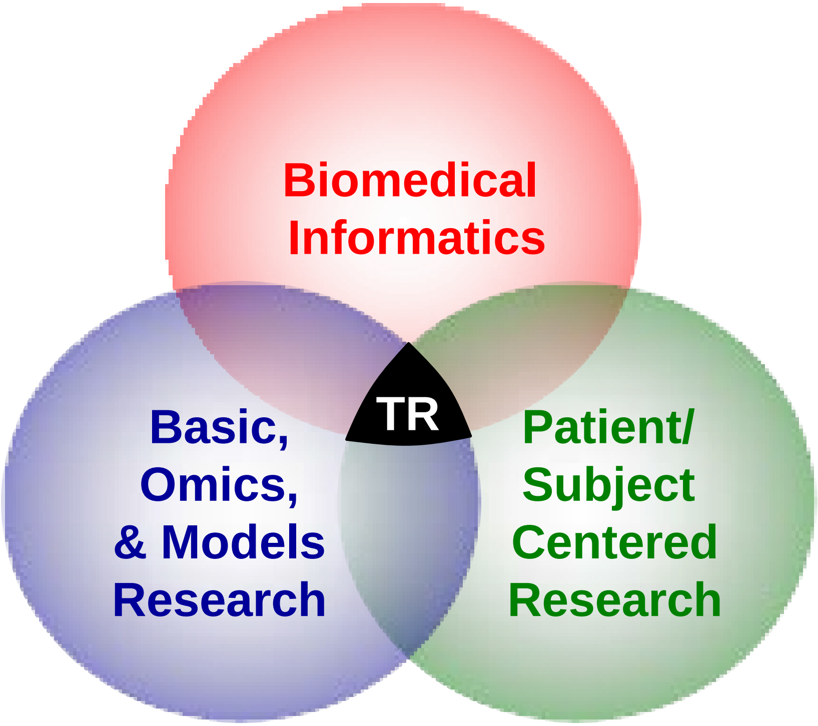
Conduct study

Publish local and combined

International and Local

Translational Research

Follow patients/subjects over time – evaluate:



Homeostatic assessments
(clinical + omic)

Changes due to medical or lifestyle interventions

Genomic & gene analyses
(one time)

Quantitative outcomes

Associate changes/outcome in quantitative assessments with genes in the context of individual genomes

Individuals Over Time

Multiple insufficiencies

Each child differs (@ first look)

Find patterns

@ M1 – A,D,H,K,L,M,N,P,Q,R

@ M2 – D,H,M,Q,R & K, L

@ M1 – B,E,G,J,O

@ M2 – B,G,J

@ M3 – B,J

Correlate with genotype (~10,000 SNPs)

17.3 million children (23.2%) in U.S. – food insecure

Child	T	A	D	E	P	F	R
D – M1	1	2	0	2	0	0	0
D – M2	1	2	1	0	1	0	0
H – M1	1	2	0	2	0	0	0
H – M2	1	1	1	0	1	0	0

Child	T	A	D	E	P	F	R
M – M1	1	2	0	2	0	0	0
M – M2	1	1	1	0	1	0	0
Q – M1	1	2	0	2	0	0	0
Q – M2	1	1	1	0	1	0	0
R – M1	1	1	0	2	0	0	0
R – M2	1	1	1	0	2	0	0

NTP
National Toxicology Program

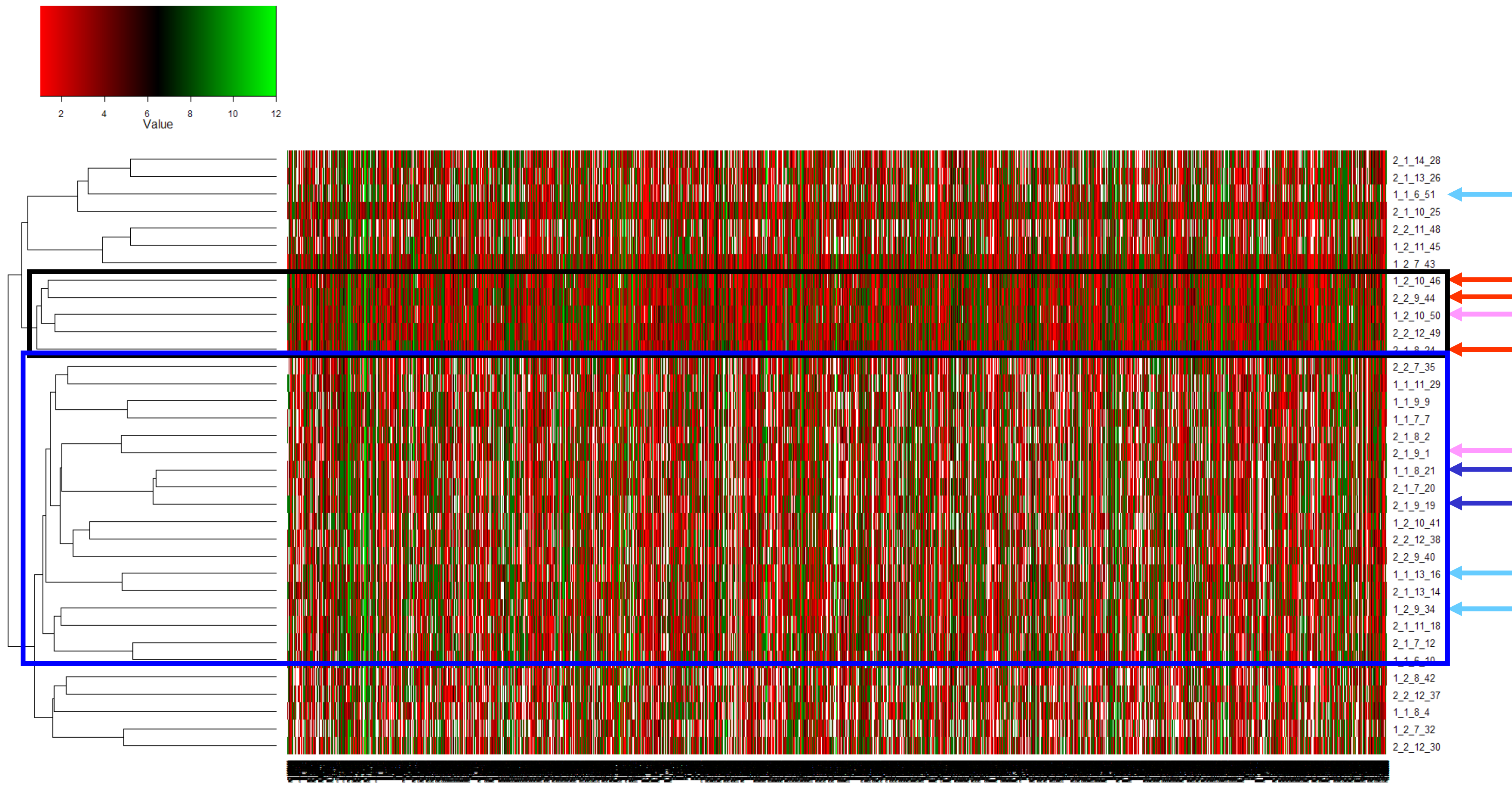
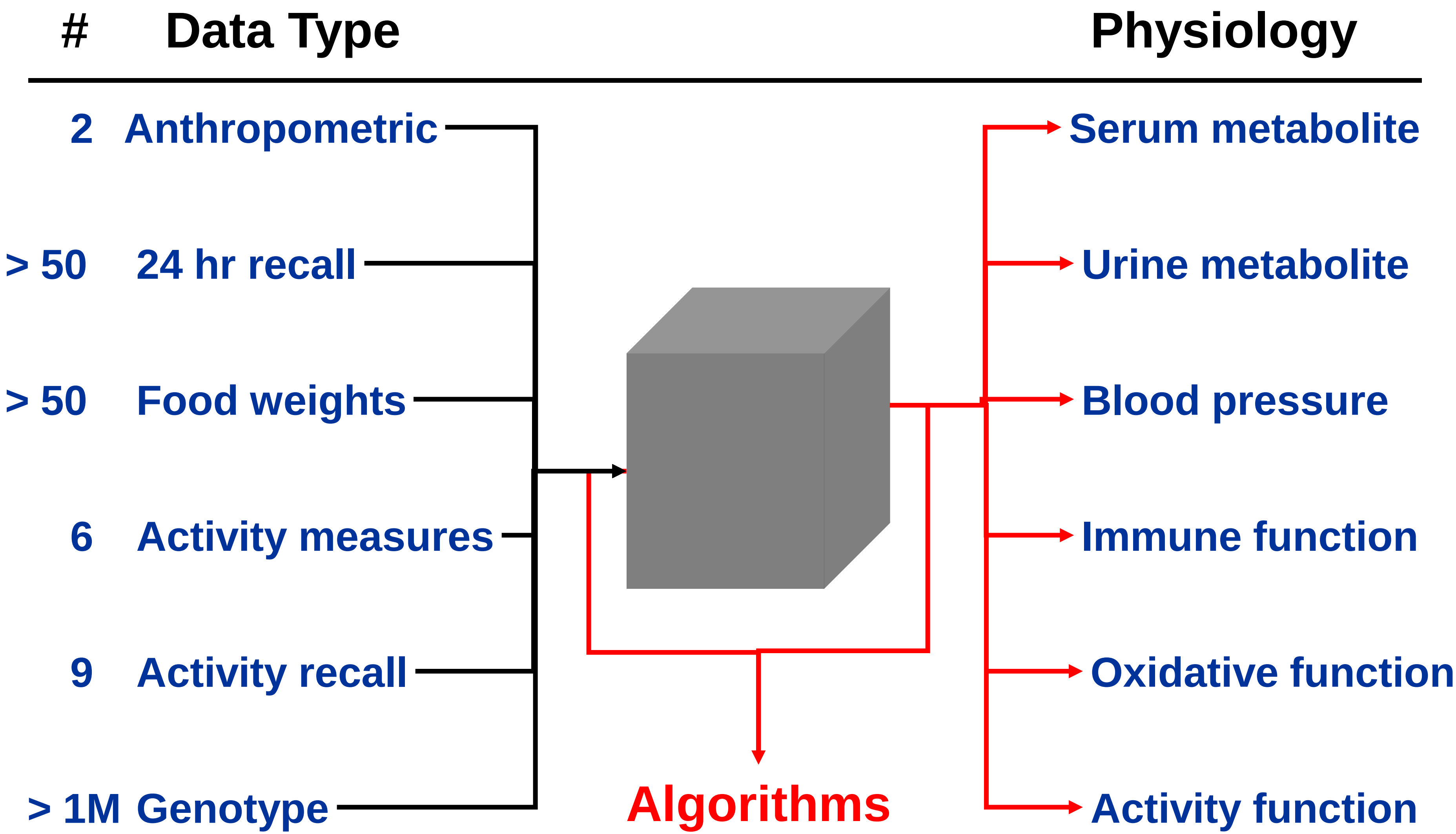
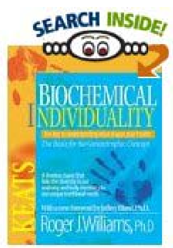


Figure 1. Clustered Subjects by SNP’s (1:A/A, 2:A/C, 3:A/G, 4:A/T, 5:A/C, 6:C/G, 7:D/D, 8:D/I, 9:G/G, 10:I/D, 11:I/I, 12:T/T)


#
Data Type
Physiology
2 Anthropometric
> 50 24 hr recall
> 50 Food weights
6 Activity measures
9 Activity recall
> 1M Genotype
Algorithms
Serum metabolite
Urine metabolite
Blood pressure
Immune function
Oxidative function
Activity function

Challenge Concept

(1956)



Many biomarkers measure homeostasis

Homeostasis has large inter-individual variation

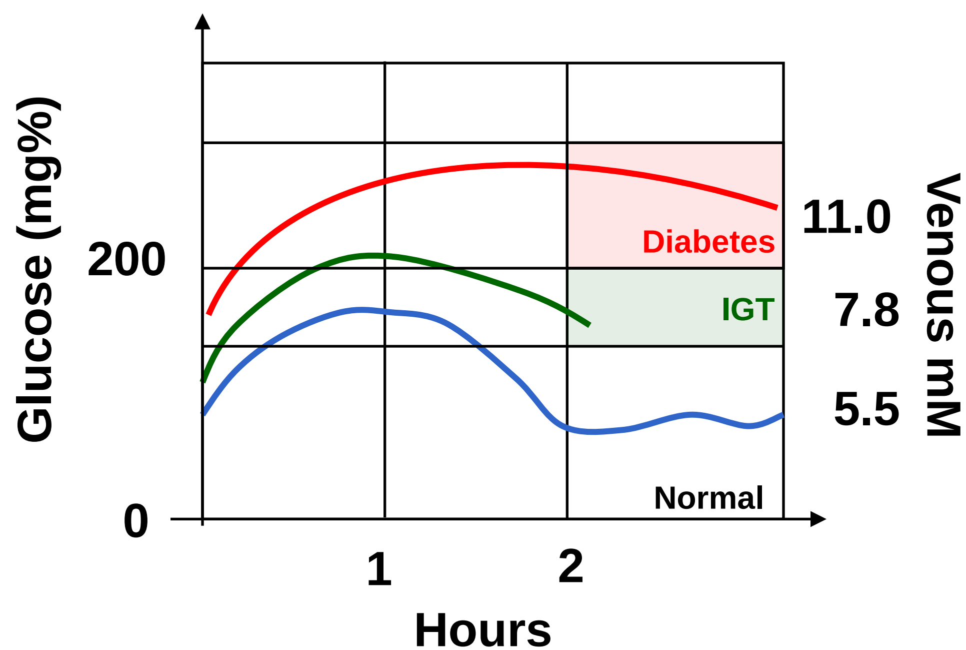
Perturb homeostasis, response measures "robustness"

Example

Oral glucose tolerance

100g (or 75g) bolus – measure glucose in venous blood over time

Measurements during or after
Other serum metabolites
Immune function
Oxidative damage
Urine metabolites



Challenge Concept

Examples
Oral glucose tolerance
Lipid challenge
Activity challenge
Oxidative stress challenge
OTC Drug challenge

Define health and biomarkers

Challenge homeostatic systems

- **Functional challenge**
- **Nutrient challenge**

Dose, kinetics, and relevant physiological measures

- **Deep genotyping and deep phenotyping**

No reference population for health

- **Compare responses in differing genetic make-ups & cultures**

Van Ommen, Keipper, Heil, Kaput, Molecular Foods Nutrition 53, 795 (2009)

Challenge Schedule